

II. Rejections under 35 U.S.C. §112, First Paragraph.

Claims 7-10, 14, 16-19, 28, 29 and 32-35 were rejected under 35 U.S.C. §112, first paragraph as containing subject matter not enabled by the specification. Applicants respectfully disagree.

At section 2 of the Office Action, the Examiner asserts that the instant specification fails to enable a RTD polypeptide comprising all or a specifically identified functional portion of SEQ ID NO:1 of the claimed invention because only one RTD polypeptide sequence is disclosed. Applicants respectfully traverse the Examiner's rejection and note that in addition to the disclosure of a representative full-length coding sequence of a RTD polypeptide, the specification describes RTD variants and teaches identification of such variants at, for instance, page 18, line 34 to page 20, line 22. Furthermore, specific structural as well as functional characteristics commonly possessed by RTD polypeptides are disclosed in the specification, for example, at page 58, line 17 to page 59, line 19. Here a RTD polypeptide is disclosed as 386 amino acids long and 41.8 kDa in molecular weight, as well as a putative signal peptide, extracellular domain, transmembrane domain and intracellular domain regions. Glycosylation sites at amino acid positions 127, 171 and 182 and two extracellular cysteine-rich pseudorepeats (Figure 1) are also described.

The claims have been amended to further clarify that the recited RTD polypeptides bind to Apo-2 ligand. For instance, Example 2 teaches a RTD polypeptide ECD binding interaction with Apo-2 ligand, as tested in immunoprecipitation assays, and Examples 3 and 4 teach RTD and RTD ECD inhibition of Apo-2 ligand function in cell culture. Given the disclosure and teachings of such assays to determine Apo-2 ligand binding, it is submitted that such assays can be readily conducted by the skilled artisan and determination of binding can be assessed without undue experimentation.

The Examiner also asserts the claimed invention encompasses those polypeptides having at least about 80% identity with SEQ ID NO:1, but because the specification does not identify those amino acid residues critical or

those which are expendable to a RTD polypeptide, a skilled practitioner cannot predict if a chimeric protein will function as a RTD polypeptide. Applicants wish to point out, as discussed above, the specification teaches structural characteristics of RTD, and putative amino acid sequences encompassed by various domains of the polypeptides. The functions of such various domains in the polypeptides of the TNFR family of proteins are appreciated by those skilled in the art, and are discussed in the specification (see for example, Background at page 4, lines 3 - 18 and page 5, lines 19 - 30). Moreover, for example at page 58, line 17 to page 59, line 4, the specification teaches the location of amino acid sequences indicative of functional domains of a RTD polypeptide. Methods for obtaining and verifying a candidate protein as a RTD polypeptide are also taught, e.g., on page 20, lines 3-22:

Once selected RTD variants are produced, they can be contacted with, for instance, Apo-2L, and the interaction, if any can be determined. The interaction between the RTD variant and Apo-2L can be measured by an *in vitro* assay, such as described in the Examples below...Generally, a ≥ 3 -fold increase or decrease in K_d per substituted residue indicates that the substituted residue(s) is active in the interaction of the native sequence RTD with the Apo-2L. Selected variants may also be analyzed for biological activity....in the *in vitro* assays described in the Examples.

The Examiner also asserts that although the term "RTD polypeptide" of claims 7-10, 14, 16-19, 29 and 32-35 is intended to encompass a variety of mammals, the specification does not adequately describe non-human forms of RTD polypeptide because "a structural formula which one would expect to be definitive of all RTD polypeptides" is not provided. Applicants respectfully traverse the Examiner's rejection. It is submitted that the claims clearly recite structural and functional limitations for the RTD polypeptides contemplated by the invention and that the artisan skilled in this art will fully appreciate the scope and meaning of the claims. Throughout the specification, Applicants have described RTD polypeptides having structural and functional properties. Furthermore, the specification teaches at, e.g., page 18, lines 5-14, identification of RTD polypeptides using routine art-known methods such as

genomic or cDNA library screening or PCR methodology. All such teachings enable one skilled in the art to identify RTD polypeptides from non-human as well as human species.

The Examiner has placed reliance on the decision in *UC Regents vs. Eli Lilly* as a standard by which to examine written description and/or enablement of the presently pending claims. Applicants point out that the '525 patent at issue in *UC Regents vs. Eli Lilly* was filed in May, 1977 --- the instant application was filed in August, 1997. It is submitted that in the 20 years since the patent at issue in *UC Regents vs. Eli Lilly* was filed, the state of the art has evolved such that with respect to the presently disclosed sequences, one skilled in the art can readily and predictably identify RTD polypeptides within the scope of the claims using for example, routine probing techniques. For the reasons discussed above, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §112, first paragraph.

At section 3 of the Office Action, the Examiner asserts that claims 33-35 are not enabled because the specification does not teach how to "produce a cell which comprises a cell". Applicants have amended the language of claims 33-35 to even further clarify the claimed host cells. Accordingly, Applicants respectfully request withdrawal of this rejection.

III. Rejections under 35 U.S.C. §112, second paragraph:

At section 4 of the Office Action, claims 7-10, 14-19 and 28-38 were rejected under 35 U.S.C. §112, second paragraph. Applicants wish to point out that prior to the present response, the pending claims under examination included claims numbered up to "35". Therefore, Applicants will direct their response in this section to claims 7-10, 14-19 and 28-35.

The Examiner asserts that the pending claims are indefinite in their recitation of the terms "RTD polypeptide" or "tumor necrosis factor receptor homolog" because the specification does not describe unique characteristics which would allow determination of whether a specific polypeptide is

encompassed by the claims. Applicants respectfully traverse the Examiner's rejection. The claims recite clear structural limitations and the amino acid and nucleic acid sequences disclosed in the specification allow a skilled practitioner to readily identify a RTD polypeptide or TNFR homologue. The specification teaches use of alignment analysis and defines at page 11, line 17 to page 13, line 7, a "RTD polypeptide" as encompassing native sequence RTD and RTD variants. Sequence properties for an RTD polypeptide are further disclosed at page 12, lines 16-27 of the specification as those having at least about 80% amino acid sequence identity. Using methods well known in the art, the skilled artisan can readily identify an RTD polypeptide by comparison of the candidate sequence to SEQ ID NO:1.

Applicants further point out that in addition to sequence composition, other structural properties well known in the art to be characteristic of TNFR homologs are also taught in the specification. For example, at page 58, line 27 to page 59, line 2, the specification discloses that:

TNF receptor family proteins are typically characterized by the presence of multiple (usually four) cysteine-rich domains in their extracellular regions -- each cysteine-rich domain being approximately 45 amino acids long and containing approximately 6, regularly spaced, cysteine residues. Based on the crystal structure of the type 1 TNF receptor, the cysteines in each domain typically form three disulfide bonds in which usually cysteines 1 and 2, 3 and 5, and 4 and 6 are paired together. Like DR4, DR5 and DcR1, RTD contains two extracellular cysteine-rich pseudorepeats (Figure 1D).

The characteristics as taught in the specification are sufficient to allow the skilled practitioner identification of the polypeptides of the claimed invention. For these reasons, Applicants respectfully request the withdrawal of this rejection.

The Examiner further asserts that claims 7-10, 14-19, 28-31 and 33-35 are indefinite because the specification does not describe how "sequence identity" is to be calculated or a specific method for determining identity. Applicants respectfully traverse the Examiner's rejection and note that in this art accepted technique for evaluating the relationship between amino acid or

nucleotide sequences, the skilled artisan understands the use and meaning of such identity values.

The specification defines identity at page 12, line 27 to page 13, line 7:

“Percent (%) amino acid sequence identity” with respect to the RTD sequences identified herein is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the RTD sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared.

This definition of “Percent (%) amino acid sequence identity” readily allows the skilled artisan to identify the sequences encompassed by the claims. In particular, the disclosure teaches that this value is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the RTD sequence. The specification also teaches that this value is obtained after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. For these reasons, Applicants respectfully request the withdrawal of this rejection.

The Examiner also asserts that claims 7 and 14 and their dependent claims, 8-10, 15-19, 28-31 and 33-35, are indefinite because they do not recite structural limitations of “an extracellular domain sequence of RTD polypeptide”. Applicants respectfully traverse the Examiner’s rejection. The specification provides the putative transmembrane domain in the RTD polypeptide of Figure 1A (SEQ ID NO:1). In one embodiment, at page 12, lines 10-15, the specification provides a “RTD extracellular domain” or “RTD ECD” as comprising amino acid residues 56 to 212 of Fig. 1A (SEQ ID NO:1). These teachings provide the skilled practitioner regions or loci within the RTD

polypeptide where the ECD resides. For these reasons, Applicants respectfully request the withdrawal of this rejection.

Information Disclosure Statement:

At section 5 of the Office Action, the Examiner indicates that legible copies of each reference listed in the IDS filed May 22, 1998 were not included with the accompanying IDS. Applicants will provide a replacement set of those references under separate cover. The Examiner is requested to consider the references prior to any subsequent action on the merits.

Respectfully submitted,

Date: April 2 1999

Diane L. Marschang

Diane L. Marschang
Reg. No. 35,600
Attorney for Applicants
Merchant & Gould
3100 Norwest Center
90 South Seventh Street
Minneapolis, Minnesota 55402
(612) 332-5300
DLM/MHC